

RESPONSE

I. Status of the Claims

Prior to the present Action, claims 8-19, 32-35, 39 and 40 were in the case. Presently, claims 8, 11, 12, 18, 19, 32 and 33 have been amended without prejudice or disclaimer to further improve their clarity and remove non-elected inventions. Claims 44-52 have been added, which are supported by the specification and claims as filed and are unified with the claims of the elected invention. No claims have been canceled.

Claims 8-19, 32-35, 39, 40 and 44-52 are therefore in the case. In accordance with 37 C.F.R. § 1.121, the pending claims are listed in the amendment section.

II. Support for the Claims

Support for the revised claims exists throughout the specification and claims of the original and parent applications. In light of the claims canceled to date, no fees should be required for the new claims. However, should any fees be deemed necessary for the new claims, such fees should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4050.001200.

Claim 8 has been amended to recite features of claim 1, on which it originally depended and is supported thereby. The phrase "(which may occur spontaneously)" has been deleted from step c.

Claims 11 and 12 have been amended to separately recite the features originally included in the "and/or" phrase, which has been deleted.

Claim 18 has been amended to make the alternative claiming even clearer.

Claim 19 has been amended to delete reference to non-elected compounds.

Claim 32 is amended to specify that (d) applies if A1 is a reversible substituent, and to insert general formula I, as set forth throughout the specification. The phrase "(which may be spontaneous)" has been deleted from step c.

Claim 33 has been amended to insert general formula XIII after (a), which is the same as, and supported by, general formula XIII in claim 32. The phrase "(which may occur spontaneously)" has been deleted from step c.

New claim 44 recites that A1 is a cis-amide bond surrogate, as supported by the specification, *e.g.*, at least at page 13, lines 25-28.

New claim 45 recites that the cis-amide bond surrogate is a tetrazole, which has support in the specification, *e.g.*, at least at page 24, lines 10-15.

New claim 46 specifies particular examples for A2, which have support in the specification, *e.g.*, at least from page 36, line 9 to page 37, line 4.

New claim 47 recites that A2 is 6-nitro-2-hydroxybenzyl, 4-nitro-2-hydroxybenzyl or 5-nitro-2-hydroxybenzyl, which have support in the specification, *e.g.*, at least in original claim 13 and in the specification at page 39, line 21.

New claims 48 and 49 have support as set forth above for claims 46 and 47, respectively.

New claims 50, 51 and 52 have been added to depend from claims 8, 32 and 33, respectively, to more definitely recite the embodiment that the ring contraction reaction occurs spontaneously. These claims are supported throughout the specification, as exemplified by original claims 8, 32 and 33.

It will therefore be understood that no new matter is included within any of the amended claims.

III. Restriction Issues

The Office has reconsidered the restriction requirement and has included additional subject matter for examination (Action at Item 1, page 2). Applicants appreciate the Examiner's holding.

IV. Specification and Drawings

The Action at Items 2-4 identifies certain informalities in the specification. Applicants respond as follows.

In regard to the sequence identifiers, Applicants respectfully point out that all required SEQ ID NOs were inserted into the specification by amendment in response to the Sequence Listing Notice of September 16, 2003, which response was filed November 17, 2003.

With reference to the abbreviations Amb and Act, these refer respectively to 3-amino benzoic acid and 3-carboxy-4-aminothiophene; the latter compound is alternatively, and perhaps more accurately, described as 3-amino-4-carboxythiophene (Ast). These abbreviations were known to those of ordinary skill in the art prior to the priority date of the present application, as shown, *e.g.*, by Smythe and von Itzstein, *J. Am. Chem. Soc.*, 116:2725-2733, 1994 (**Exhibit A**) and by Meutermans *et al.*, *Letters in Peptide Science*, 4:79-84, 1997 (**Exhibit B**), copies of which are enclosed. The specification at pages 25 and 65 has been revised accordingly.

As to Figure 5, a clean copy of Figure 5 showing the identifiers "Peptide 1D" and "Peptide 1E" is submitted herewith.

V. Objection to Claim 19

The Action at Item 5 objects to claim 19 as containing non-elected compounds of formula (a). Claim 19 has been amended to delete the reference to the non-elected compounds.

VI. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The Action at Items 8-16 rejects claims 8-19, 32-35, 39 and 40 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite on various grounds. Although Applicants respectfully traverse in part, the Action's concerns are addressed.

A. Item 8

At Item 8, all claims are rejected as depending on a canceled claim. Applicants apologize for this oversight, which was discussed with the Examiner via telephone. Claim 8 has been amended to recite the omitted features of claim 1, on which it originally depended.

B. Item 9

The proper test of definiteness is whether, in the light of the teachings of the prior art and of the particular application disclosure, the claims set out and circumscribe, for one possessing an ordinary level of skill in the pertinent art, a particular area with a reasonable degree of particularity. *In re Moore*, 169 USPQ 236 (C.C.P.A. 1971), emphasis added.

In response to the rejection in Item 9, Applicants respectfully point out that, in light of this application disclosure, particularly the definition of "monomer" in the specification from page 22, line 21 to page 23, line 21, one of ordinary skill in the art would have no difficulty in understanding how a peptide can be only one monomer.

The Office also questions whether it is the initial formation of a larger flexible ring, or the ring contraction reaction itself, which occurs spontaneously. Applicants respectfully submit that it is clear from the specification, and in particular from Example 2 at pages 35 to 38, that the ring contraction takes place once the larger ring has been formed, and that this ring contraction may occur spontaneously, or as a response to heating or treatment with chemicals. Moreover, other ring contraction auxiliaries in addition to Hnb are disclosed, *e.g.*, see pages 36-37 of the

specification. Nonetheless, claims 8, 32 and 33 have been amended to remove the optional phrasing regarding spontaneous ring contraction, which is now even more definitely recited in the separate dependent claims 50, 51 and 52, thus addressing the Action's concerns.

C. Item 10

At Item 10, claims 8 and 32 are rejected as having insufficient antecedent basis for General Formula I. These oversights are herein corrected by amendment.

D. Item 11

Claims 11 and 12 are rejected for using the term "and/or". In response, Applicants respectfully point out that it would be clear to those of ordinary skill in the art in light of the specification that the term "and/or" in claim 11 means that either A1, A2, or both A1 and A2 is left attached to the peptide. Similarly in claim 12, one of ordinary skill in the art would understand this term to mean that either A1, A2, or both A1 and A2 is subsequently linked or derivatized. Nonetheless, claims 11 and 12 have been amended to separately recite these features, thus addressing the concerns regarding "and/or".

E. Item 12

At Item 12, claim 12 is rejected as allegedly being indefinite in regard to the term "derivatized". In response, Applicants respectfully point out those of ordinary skill in the art would clearly understand the term "derivatized" when read in light of the specification. The rejection is therefore improper, as it is the function of the specification and not the claims to set forth operable parameters. As stated by the P.T.O. Board of Appeals:

It is by now well established that it is the function of the descriptive portions of the specification and not that of the claims to set forth operable proportions and similar process parameters and that claims are not rendered indefinite by the absence of the recitation of such limitations.

Ex parte Jackson, 217 USPQ 804, 806 (PTO Bd. App. 1982); emphasis added.

In particular, one of ordinary skill in the art would understand that a free functional group provides the ability for synthetic manipulation or derivatization at this functional group. It would be further understood that a wide variety of such reactions is possible, and claim 12 would not be thought unclear by not reciting any particular derivatization. Examples of derivatization understood to be within claim 12 include:

1. Methylation, for example by treatment with diazomethane when A1 or A2 is Hnb; this may routinely be affected in order to improve yields following photolysis;
2. Oxidation of the thiol to a disulphide-linked entity, for example when A1 or A2 is $\text{CH}_2\text{CH}_2\text{SH}$, as shown in Scheme 6 at page 38 of the specification; and
3. Alkylation on to resin when A1 or A2 is either Hnb or $\text{CH}_2\text{CH}_2\text{SH}$.

Applicants respectfully refer to the passage in the specification from page 15, line 19 to page 16, line 4. Such derivatization is well-known in the art, and is widely used in combinatorial chemistry. In this field, it has been termed a "library from library" approach and is well understood in the art, see, for example, Ostrech *et al.*, *Proc. Natl. Acad. Sci. USA*, 91:11138-11142, 1994 (**Exhibit C**).

F. Item 13

With reference to Item 13, the Action appears to be reading claim 18 to mean that the three alternatives presented are actually sequential steps. In contrast, those of ordinary skill in the art would clearly understand that the options recited are alternatives. Nonetheless, claim 18 has been amended to make the alternative phrasing even clearer.

G. Item 14

Item 14 rejects claims 32 and 39 in regard to reversible and non-reversible substituents. The rejection is overcome by amending claim 32 to further emphasize that sub-paragraph (d) applies if A1 is a reversible substituent.

H. Item 15

At Item 15, claim 33 is rejected as having insufficient antecedent basis for General Formula XIII and General Formula I. These oversights are herein corrected by amendment.

I. Item 16

Finally, claims 33-35 and 40 are rejected as not defining the terms A1, A2, P and L. The rejection is overcome by amending claim 33 to clearly define P, A1, A2 and L.

Item 16 also rejects claim 33 as allegedly indefinite in regard to the term "which may occur spontaneously". This has been addressed above in regard to Item 9, which shows that the term is clear in light of the specification, particularly in Example 2, which shows that the ring contraction takes place once the larger ring has been formed, and that this ring contraction may occur spontaneously, or as a response to heating or treatment with chemicals.

In addition, the rejection under 35 U.S.C. § 112, second paragraph is misplaced as the inclusion of optional components or steps in claims has long been acceptable. For example, the P.T.O. Board of Patent Appeals and Interferences overturned an examiner's rejection of the phrase "optionally containing a polyamine", finding that optional aspects did not render the claims indefinite. *Ex parte Wu*, 10 USPQ2d 2031 (Bd. Pat. App. & Inter. 1989).

Wu further supports Applicants' position and maintains the line of reasoning set forth above, stating "in rejecting a claim under the second paragraph of 35 U.S.C. 112, it is incumbent on the examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims". 10 USPQ2d at 2033.

All claims were therefore definite as written under the applicable case law. Nonetheless, claims 8, 32 and 33 have been amended to remove the optional phrasing regarding spontaneous ring contraction, which is now even more definitely recited in the separate dependent claims 50, 51 and 52, thus addressing the Action's concerns.

The § 112, second paragraph rejections are therefore overcome and should be withdrawn.

VII. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 8-19, 32-35, 39 and 40 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Although Applicants respectfully traverse, the rejection is overcome.

Applicants respectfully submit that the written description rejection is *prima facie* improper as it ignores the details in the specification, as would be understood by those of ordinary skill in the art. The Action also does not give sufficient credit to the written description support in the whole of the specification, and has improperly focused merely on the working examples. The rejection also misapplies the written description guidelines and controlling case law.

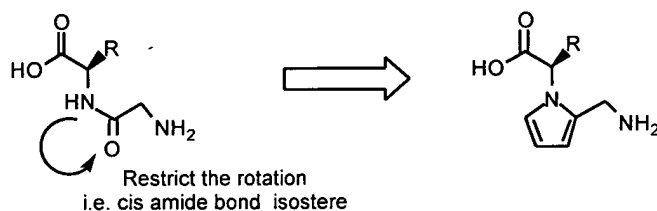
In contrast to the assessment in the Action, one of ordinary skill in the art would recognize that the description in the specification conveys that the inventors did indeed have possession of the invention as defined in the claims. Although the claims are supported by specific working examples, those of ordinary skill in the art would view the specification as describing methods to make other cyclic peptides, using alternative species of A1 and A2, and alternative locations of the linker L. For example, the specification clearly states at page 13, lines 18-21 that the linker may be attached to *any* atom of the peptide, but is preferably attached to a backbone nitrogen or to an atom in the side chain of the monomer. Thus, the specification

properly describes a *generalized* method, which is not limited to any specific target peptide, and the written description rejection has been misapplied.

One of ordinary skill in the art would understand the specification to provide the written description required to support the A1 terminology in the claims, both from the general description, and the particular examples set forth, such as:

N- α -tert-butyloxycarbonyl (Boc), at page 10, line 9;
N-(2-hydroxy-4-methoxybenzyl) (Hmb), at page 10, line 12; Table 3, Table 4;
N-Me, at Table 3, page 31;
6-nitrobenzyl-2-hydroxy (HnB), at page 51, line 34; and
Tetrazole, at page 24, line 11

In addition, the following pyrrole has been evaluated as a *cis* amide bond surrogate:

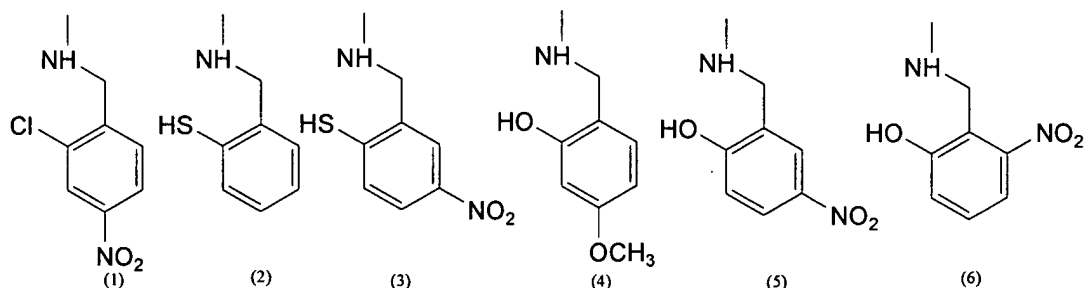


Those of ordinary skill in the art would also understand the specification to provide the written description required to support the A2 terminology in the claims, again from the general description, and the particular options set forth, such as:

page 11, Scheme 4
page 36, the structures between line 11 and 14
page 37, the structures at top of the page
page 37, line 19, the ethane thiol substituent (Scheme 6)
page 39, line 21, the 5-nitro-2-hydroxybenzyl substituent
page 41, line 5, the 6-nitro-2-hydroxybenzyl substituent

The ordinary skilled artisan would further understand the specification to provide the written description for a number of aromatic auxiliaries, such as those illustrated below. The

specification therefore again provides the description required to support the pending claims, as would be understood by those of ordinary skill in the art.



Structures 5 and 6 are disclosed in the specification as being used as A2, and structures 4 and 6 are disclosed as having been used as A1. One of ordinary skill in the art would clearly understand the specification as describing structures 2 and 3 for use as *either* A1 *or* A2. Structure 1 is a control structure, which could be used for A1, although it is not used for A2.

With reference to the position of the linker L, one of ordinary skill in the art would understand the specification to provide the written description required to support the pending claims, both from the general description and the particular examples set forth. The specification describes that the linker L may be attached to any atom of the peptide, as stated above. The specification also describes the attachment of the linker to the carboxyl-terminus of the first amino acid, as shown in Example 6 at page 84, and to the nitrogen atom of the first position, as shown at page 117 line 9.

Accordingly, and in contrast to the Action at page 5, one of ordinary skill in the art would understand that the specification describes a genus of variants for A1 and A2, and alternative locations of the linker L, in a manner effective to support the pending claims. The specification thus provides a written description that supports the claims as required by 35 U.S.C. § 112, first paragraph and in accordance with the case law cited in the Action.

In particular, Applicants comply with *Vas-Cath Inc. vs. Mahurkar*, 19 USPQ2D 1111 (Fed. Cir. 1991), as the literal written description support for the present claims has existed in the claims and the present specification throughout. The *Vas-Cath* court explains that the written description requirement might not be satisfied where:

"the specification discusses *only* compound A and contains no broadening language of any kind. This might very well be enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B and C has not been described"

19 USPQ2D at 1115.

The above situation does not apply to the present case. The specification has always contained the language required to support the claims which, although supported by particular working examples, is not so limited to the working examples such that it could be assessed to describe only the compounds therein. Applicants also note that in *Vas-Cath*, the Federal Circuit *reversed* the initial holding of the lower court that the claims were not supported by the specification and drawings.

Applicants have studied the revised interim written description guidelines referenced in the Action bridging pages 6 and 7, as well as the final written description guidelines that supersede such interim guidelines. The present application complies with the final written description guidelines by describing the claimed invention with sufficient descriptive means, including words, structures, figures, diagrams and formulas, and with working examples of a representative number of species within the claimed genus, coupled with a teaching that correlates the working examples with the generic teachings and the text of the claims.

The § 112, first paragraph rejection is therefore overcome and should be withdrawn.

VIII. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and enclosed documents, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner Kam have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,
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Date: January 26, 2005